

# Unlocking PTSD: From Single Cells to Improved Therapeutics

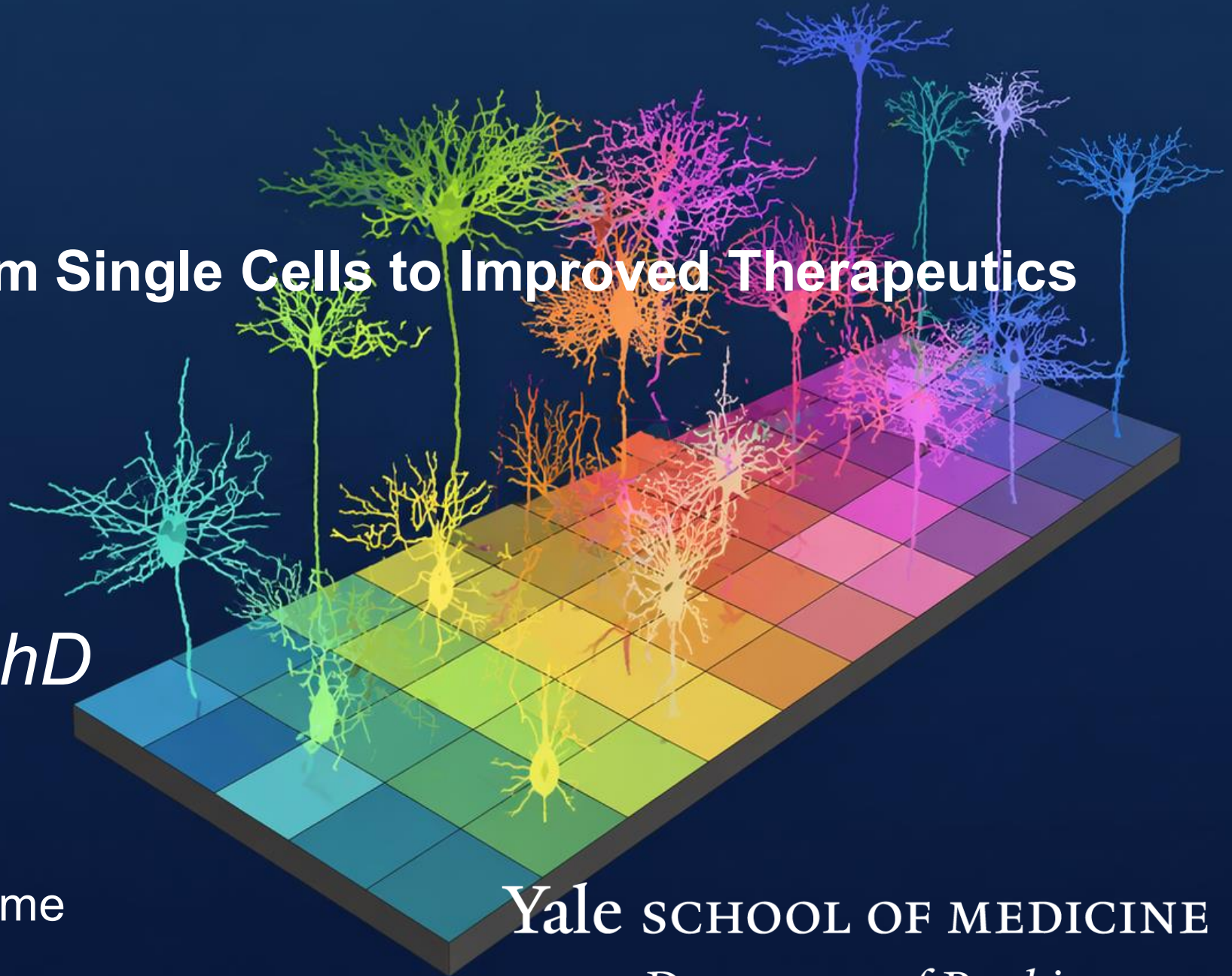
BBRF Webinar  
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<https://www.girgentilab.org/home>

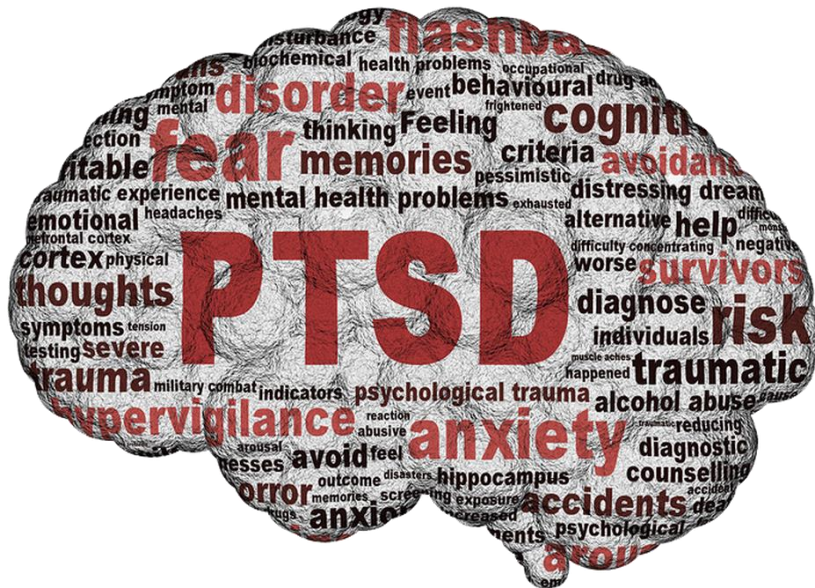


Yale SCHOOL OF MEDICINE  
*Department of Psychiatry*

## PTSD is more than a memory of trauma

**Post-traumatic stress disorder (PTSD)** is a psychiatric disorder, characterized by re-experiencing, avoidance, negative emotions and thoughts, and hyperarousal in the months and years following exposure to severe trauma.

*These symptoms reflect changes in how the brain processes threat, memory, emotion, and safety.*



## KEY PTSD SYMPTOMS

## 1

## RE-EXPERIENCING THE TRAUMATIC EXPERIENCE

- Flashbacks
- Nightmares
- Repetitive Images
- Physical Sensations like sweating, pain, or trembling

## 2

## SITUATIONAL AVOIDANCE

- Avoiding thoughts, feelings, places, and people that trigger reminders of the traumatic event

## 3

## AROUSAL AND REACTIVITY

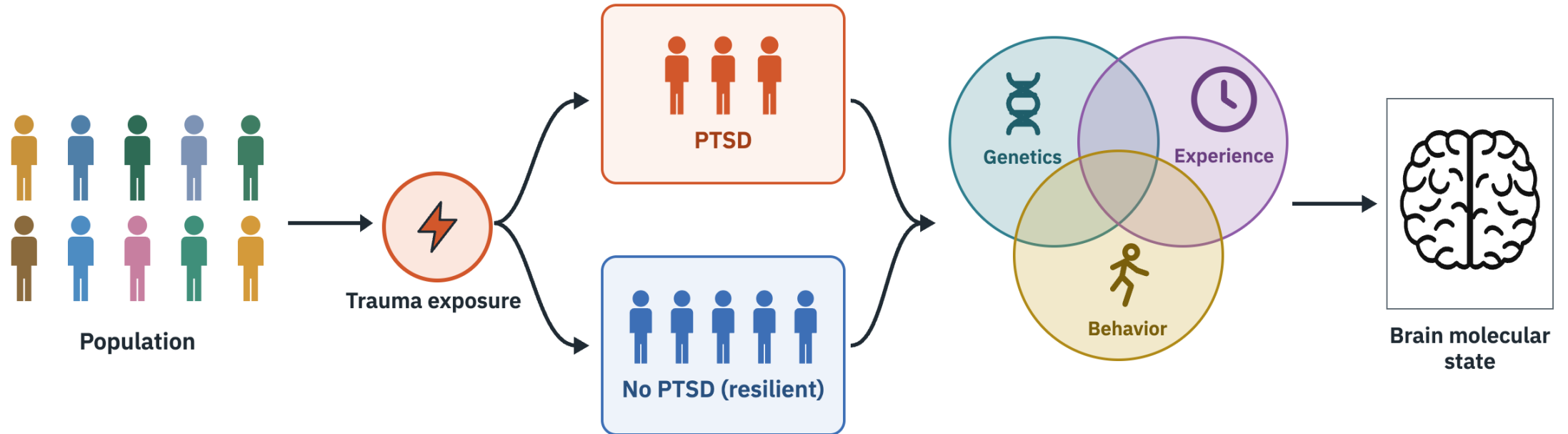
- Irritability and angry or aggressive outbursts
- Feeling tense or “on guard”
- Difficulty sleeping or staying asleep

## 4

## COGNITION AND MOOD

- Difficulty concentrating
- Having trouble remembering key elements of the traumatic event
- Feeling anger, guilt, or shame

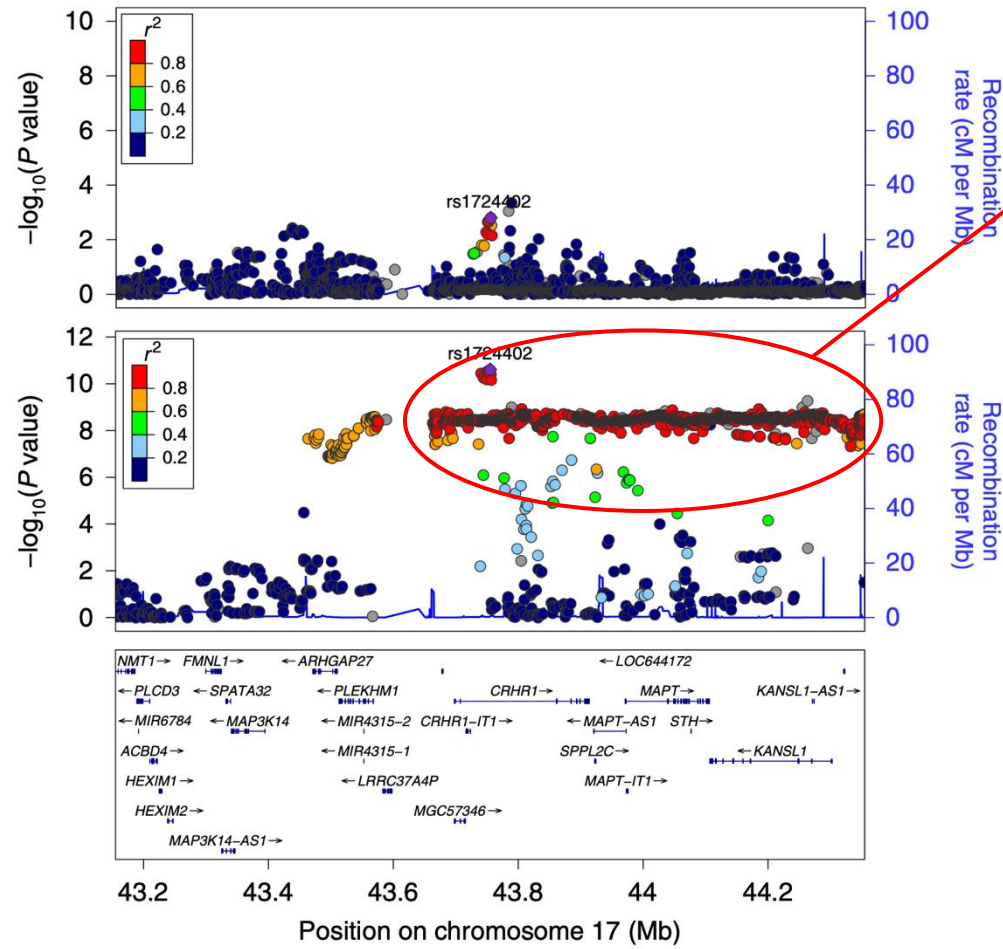
# Why does trauma affect some people differently than others?



*How does trauma change the brain- and why are some brains more vulnerable than others?*

# Our DNA contains clues about PTSD

Regional Manhattan Plot: PTSD



But what does the DNA actually do?

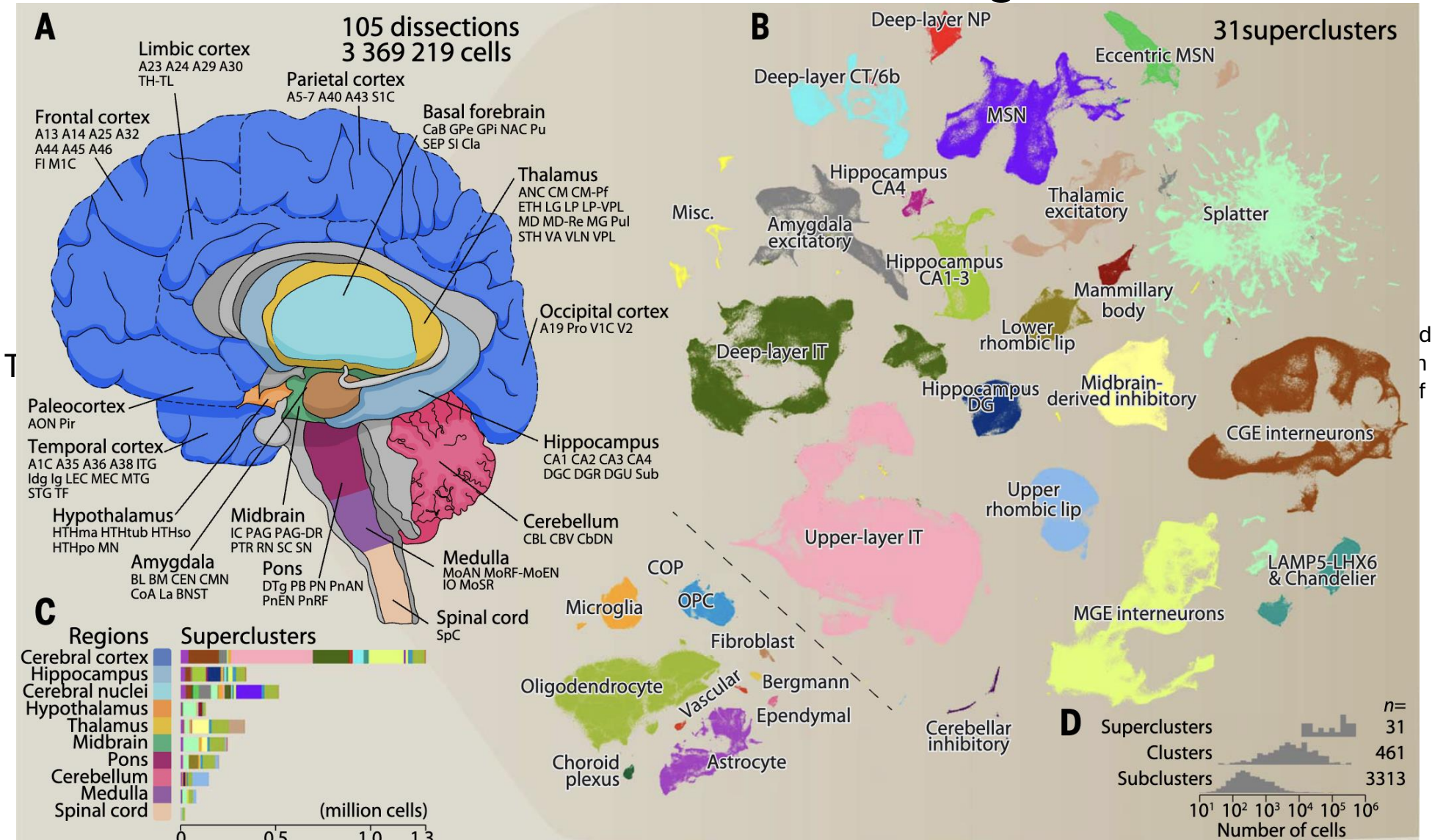
Which gene?

Which brain cells?

What changes inside the cell?

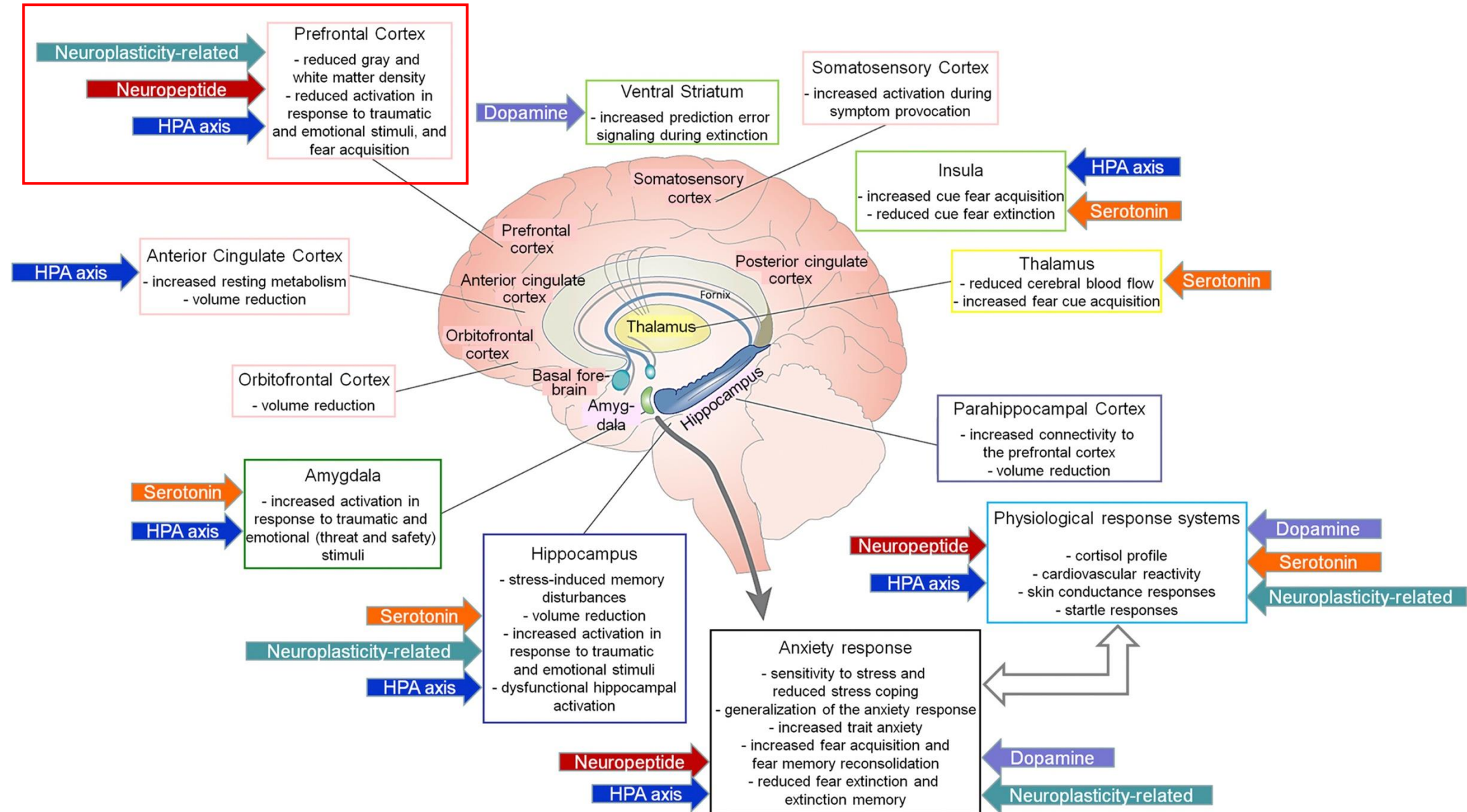
Can we change it back?

## The brain isn't one thing...



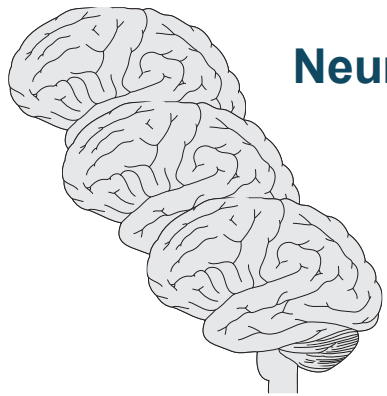
**The brain is not one cell type. Disease biology is not one molecular signal.**

# Finding Vulnerable Cell Types in Post-traumatic Stress Disorder



# Data Overview

**Goal:** Use single cell and cell type-specific multi-scale atlases of human brain regions to answer questions about the neurobiology of PTSD.



Neurotypical

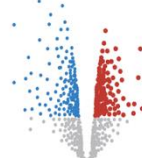
MDD

PTSD

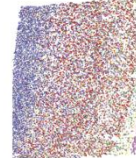
Cell Type Clustering



Differential Expression



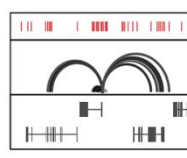
Spatial Validation



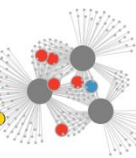
Cell-to-Cell Communication



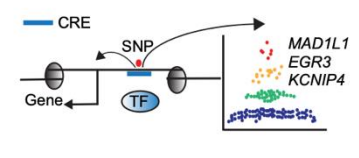
Peak-to-Gene Links



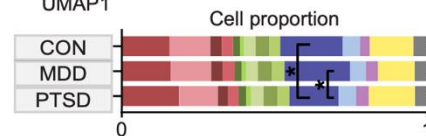
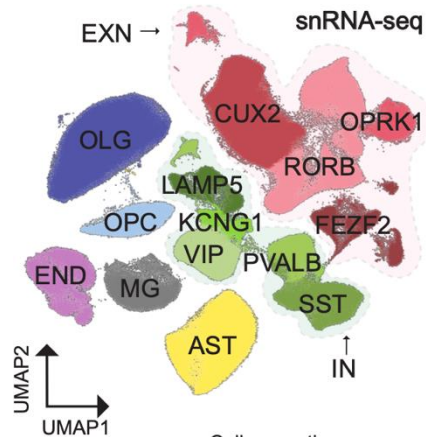
TF Network



GWAS Fine-Mapping

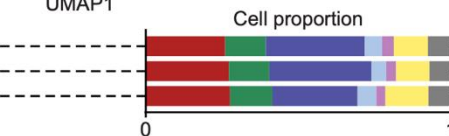
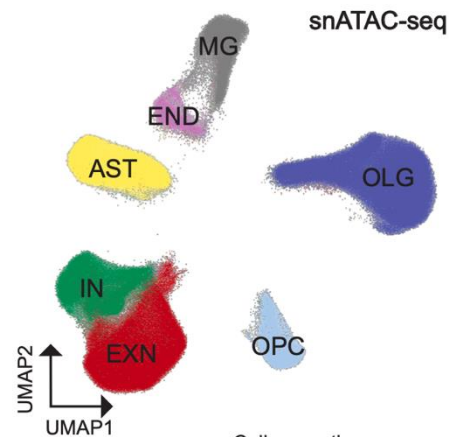


105 samples, 935,371 cells  
38 CON, 32 MDD, 35 PTSD



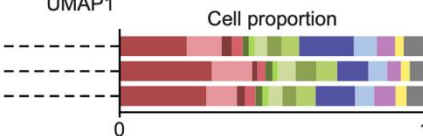
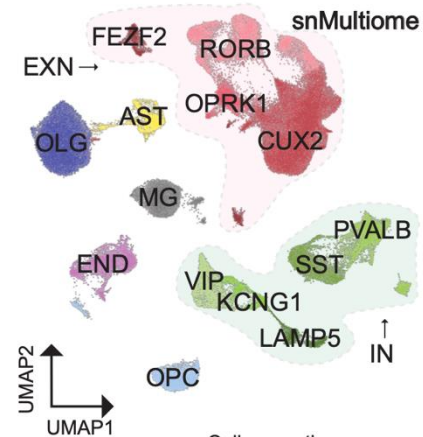
c

94 samples, 473,033 cells  
34 CON, 31 MDD, 29 PTSD



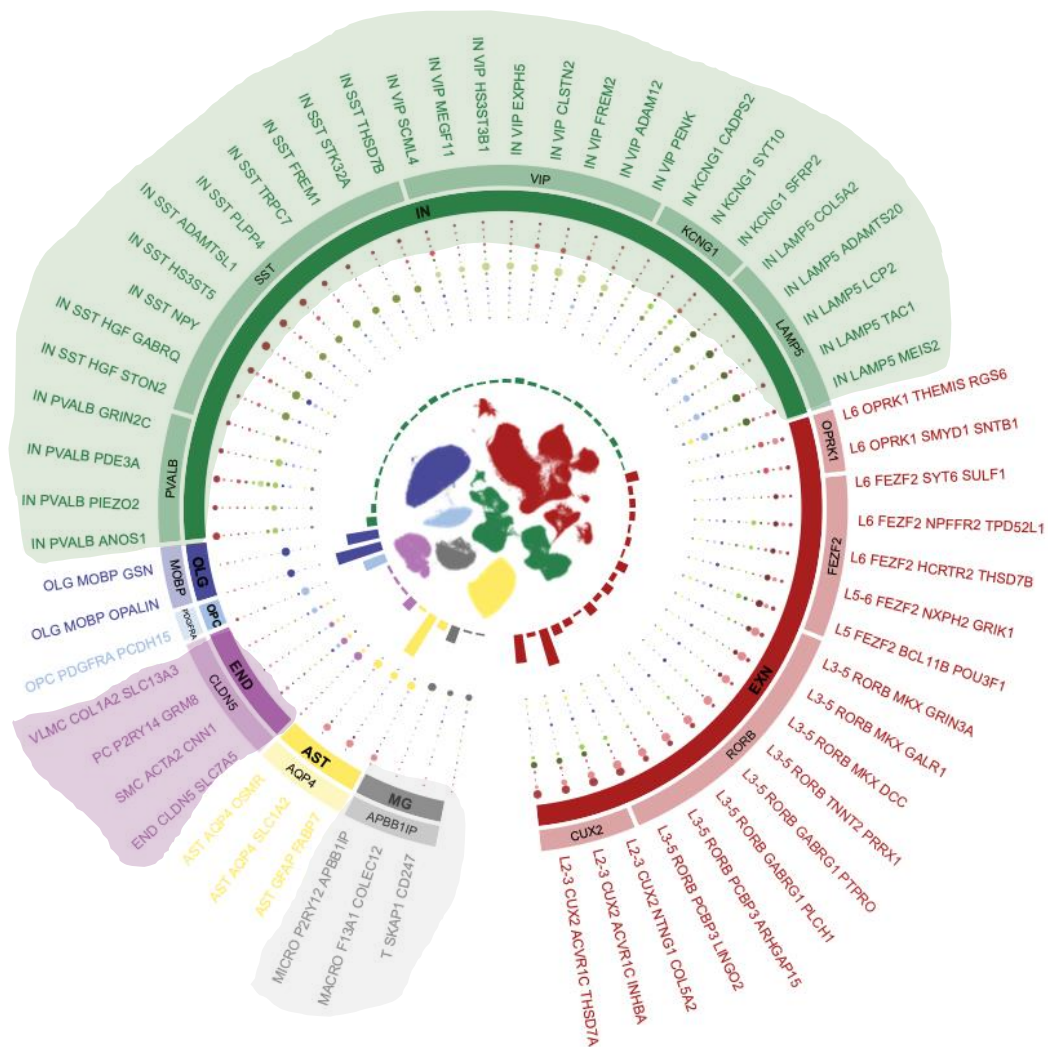
d

25 samples, 119,431 cells  
9 CON, 4 MDD, 12 PTSD

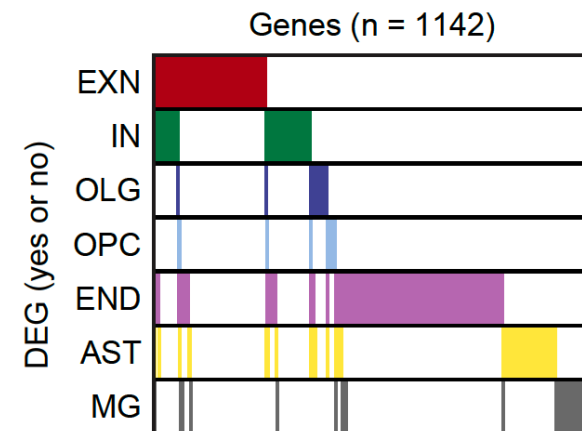


Hwang, Skarica, Xu et. al. 2025

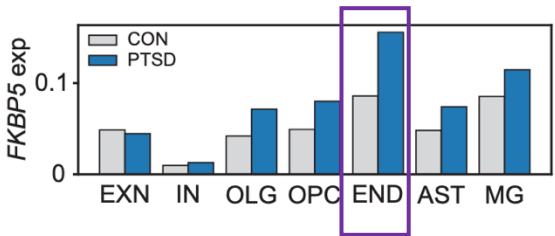
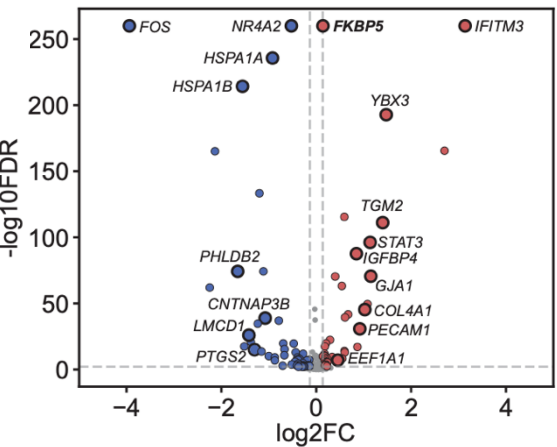
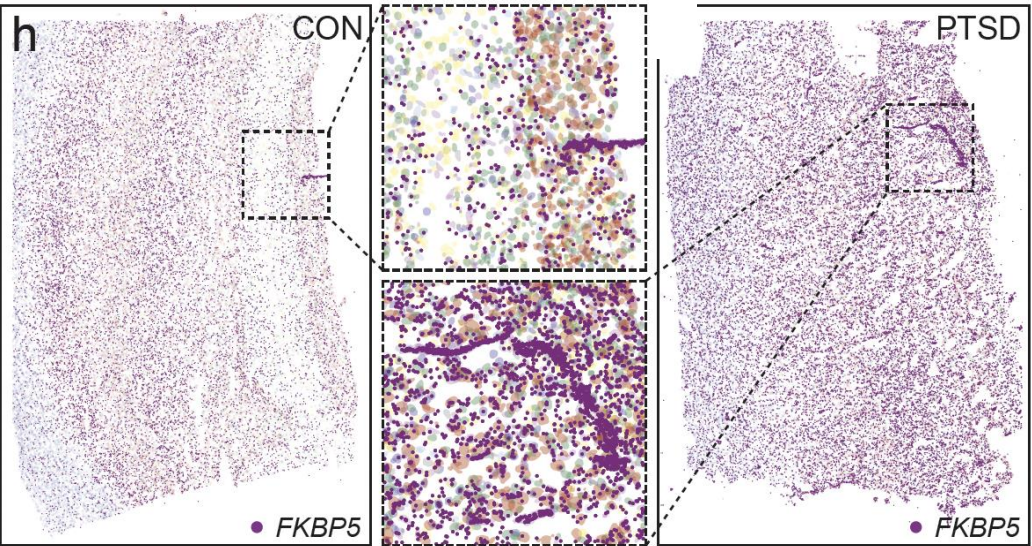
**PTSD results in large changes to genes in neurons, blood vessel cells and immune cells**



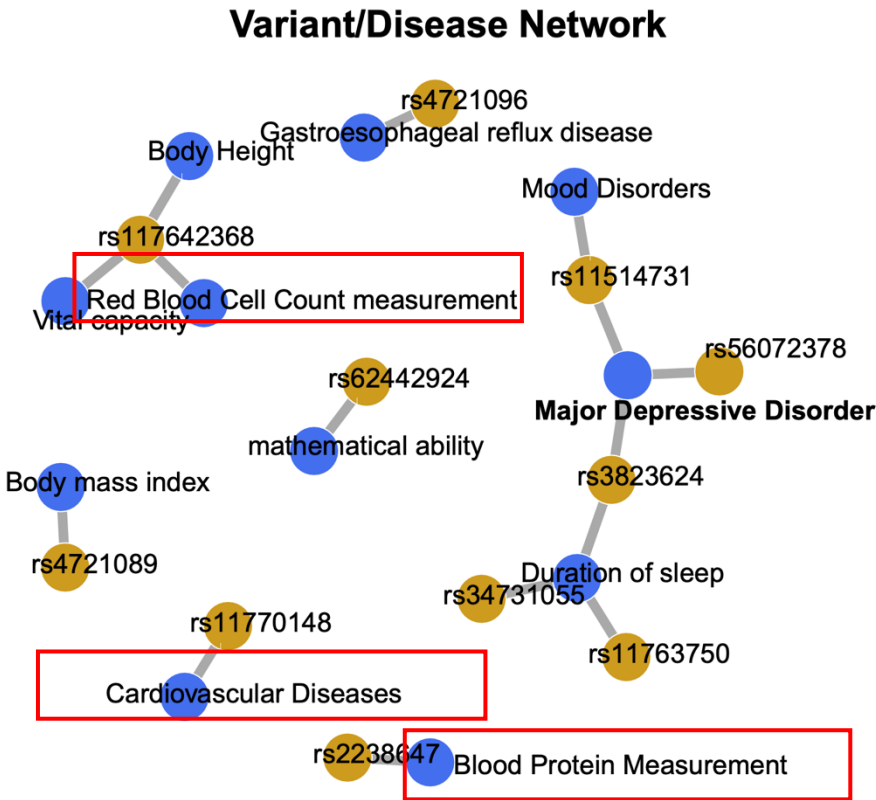
|     | Down | Up  |     | Down | Up  |       |
|-----|------|-----|-----|------|-----|-------|
| EXN | 68   | 226 | EXN | 30   | 187 | CUX2  |
| IN  | 102  | 78  |     | 24   | 51  | RORB  |
| OLG | 38   | 12  |     | 17   | 22  | FEZF2 |
| OPC | 16   | 13  |     | 26   | 60  | OPRK1 |
| END | 346  | 162 | IN  | 44   | 41  | LAMP5 |
| AST | 66   | 116 |     | 31   | 15  | KCNG1 |
| MG  | 95   | 20  |     | 23   | 28  | VIP   |
|     |      |     |     | 15   | 20  | SST   |
|     |      |     |     | 28   | 38  | PVALB |



# Vascular Pathophysiology in PTSD: disruption in stress hormone signaling

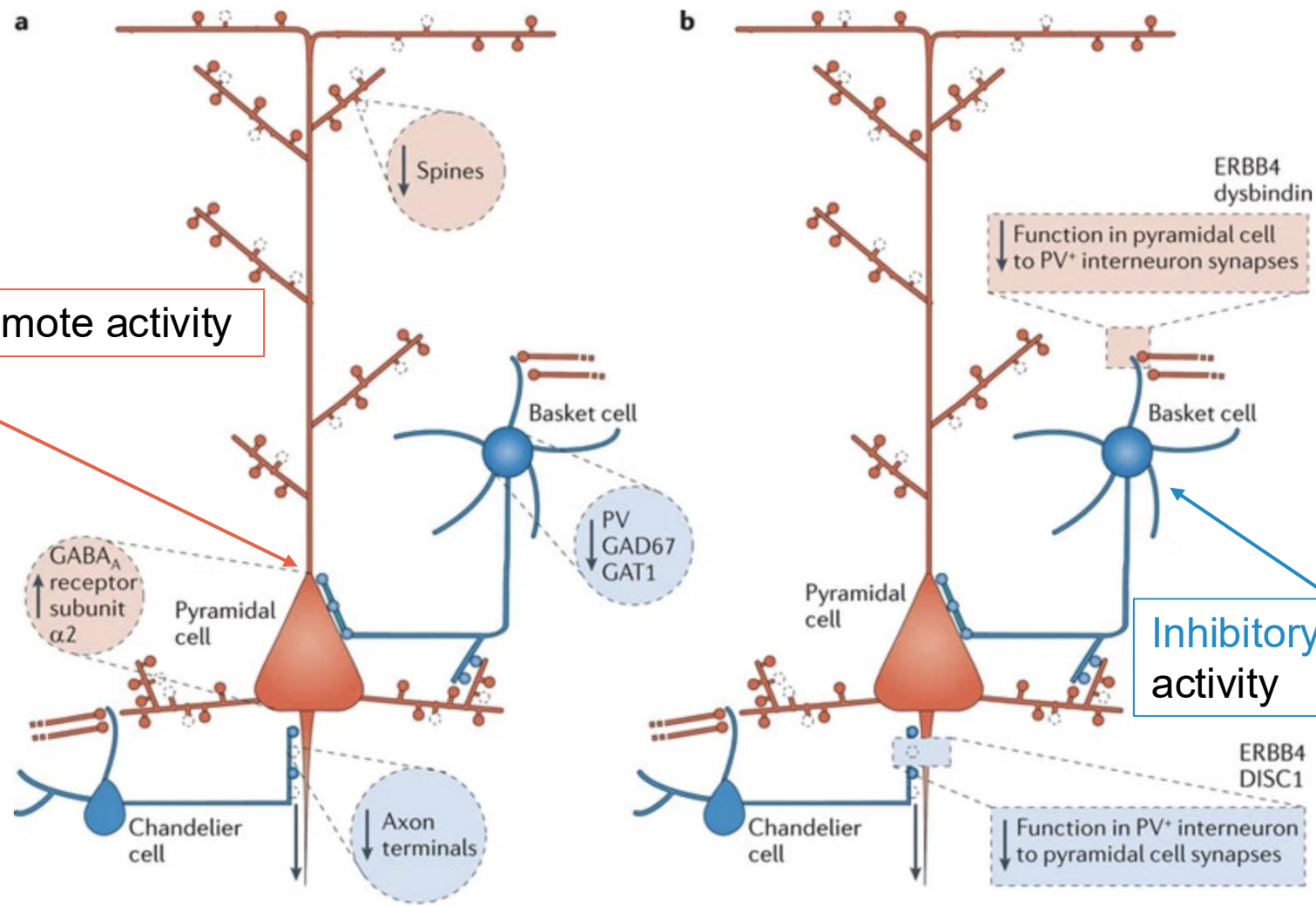


Hwang, Skarica, Xu et. al. 2025



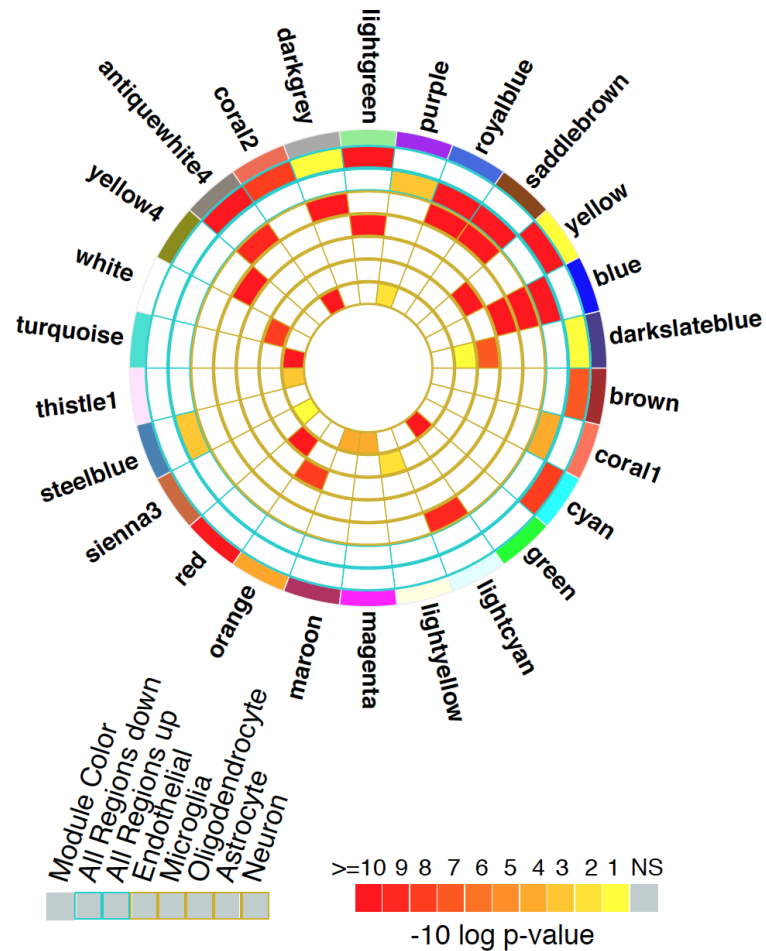
Li, et. al. 2025

## Some cells act like the brain's “brakes”

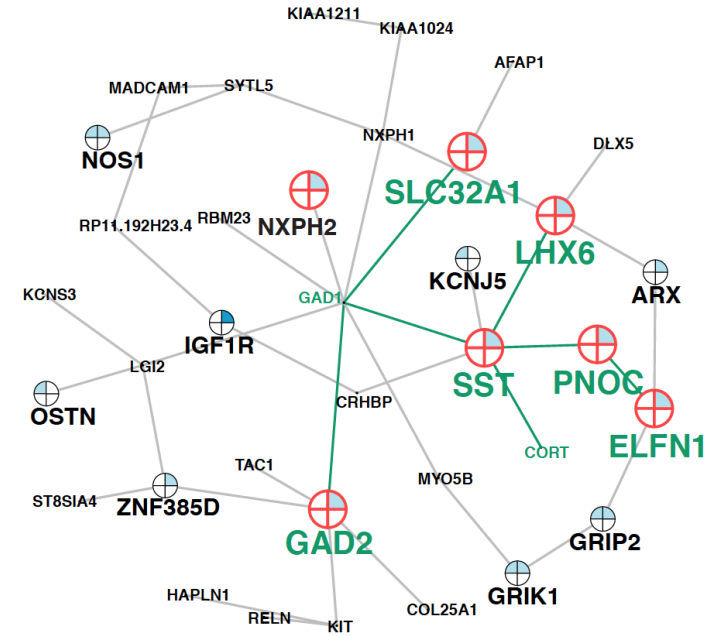


*The brain needs both. Too much excitation can be destabilizing; too much inhibition can suppress important signals.*

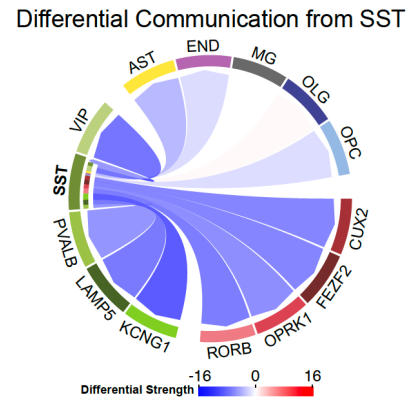
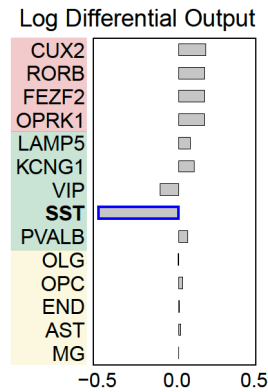
# Network alterations in the PTSD transcriptome implicate interneuron vulnerability



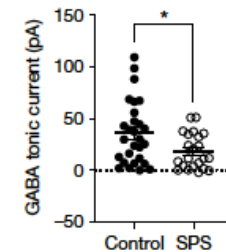
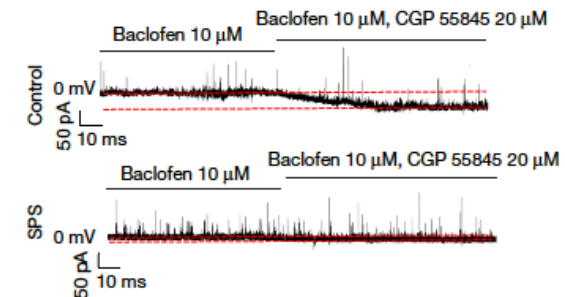
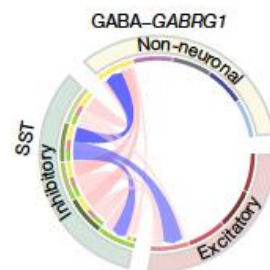
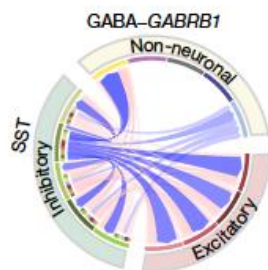
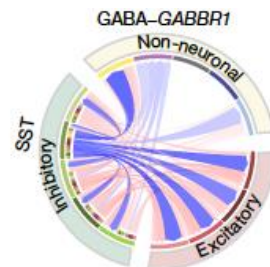
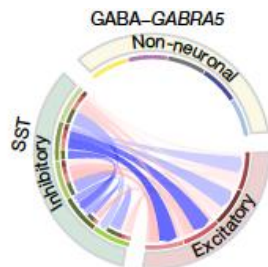
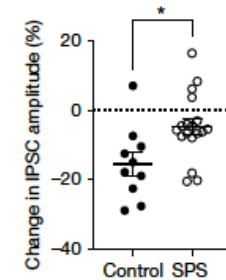
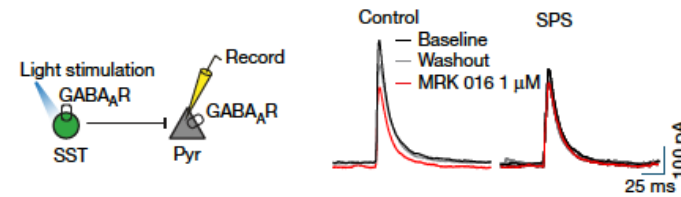
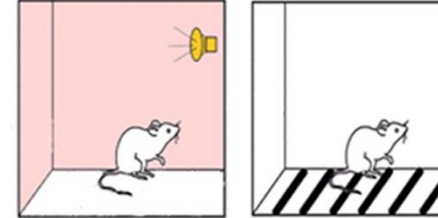
**coral2: neuronal**  
32 genes, 15 DEGs



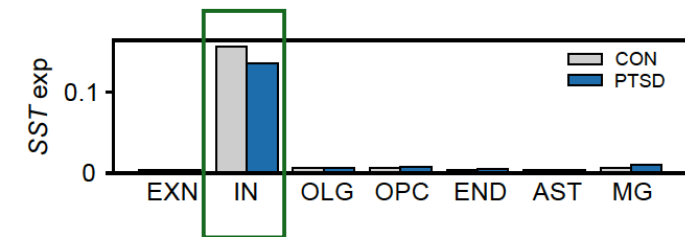
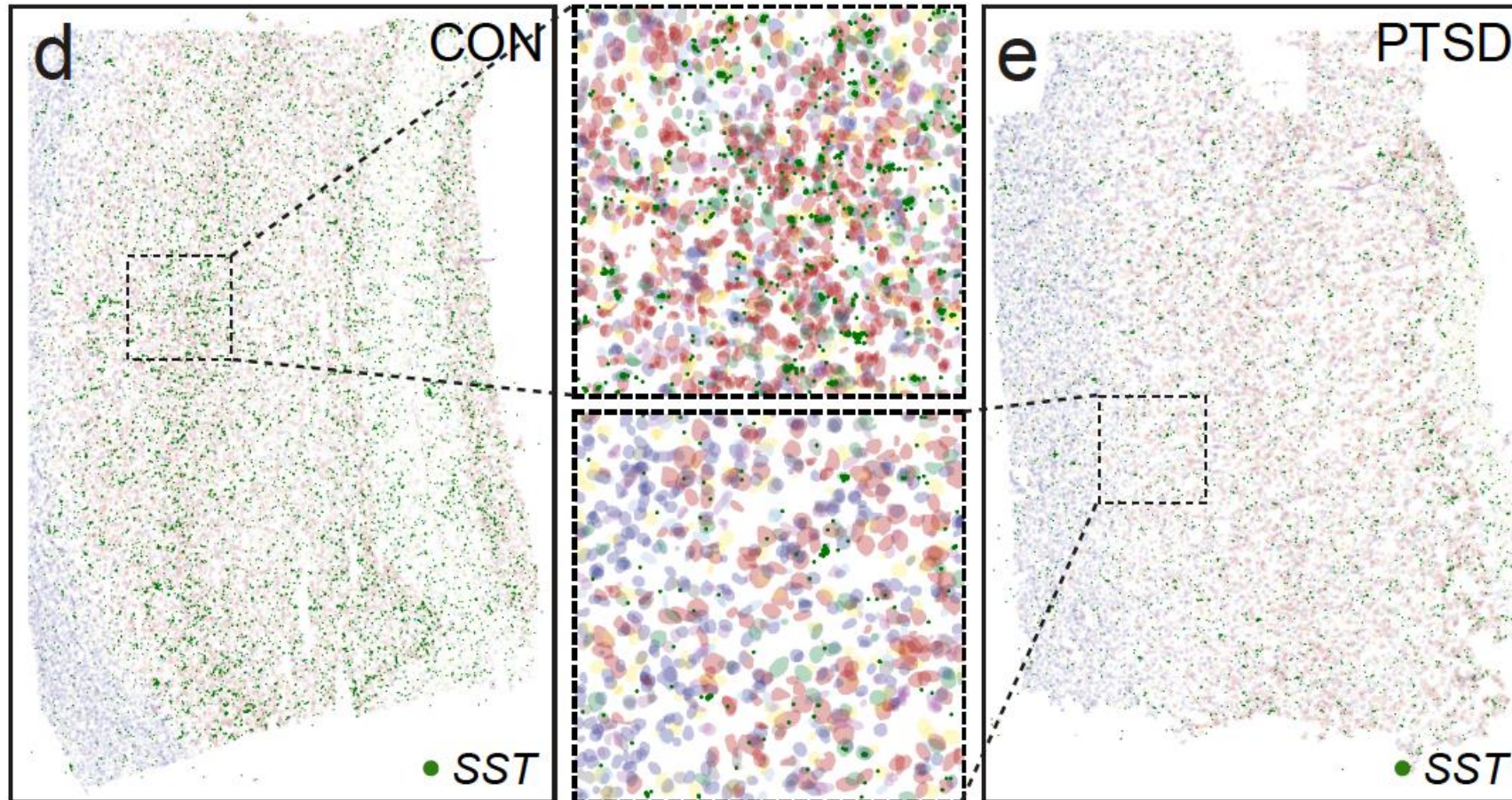
# PTSD results in disruptions in cell-to-cell communication from interneurons



## Traumatic Stress Mouse Model



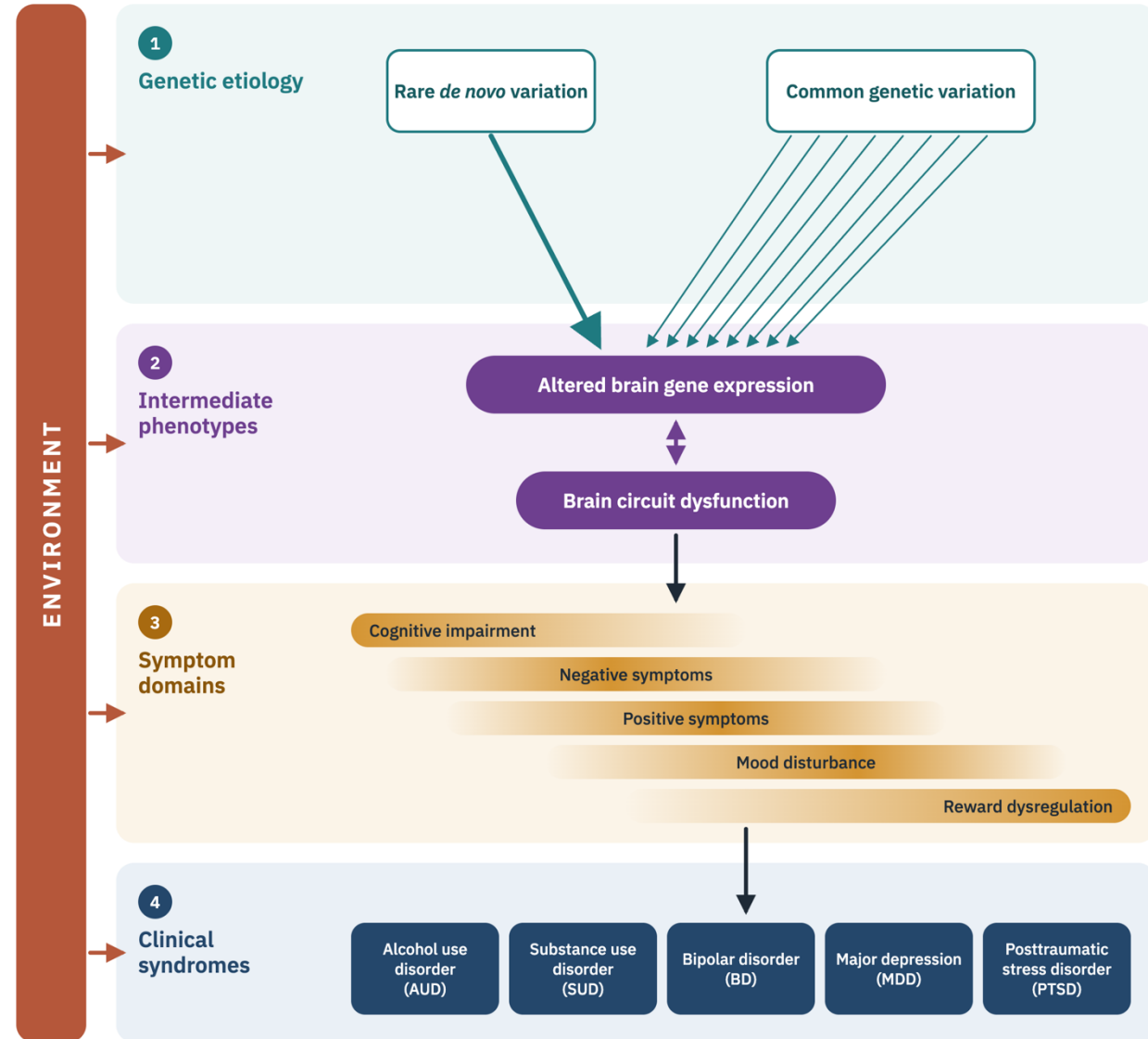
# Somatostatin expression levels decrease during PTSD



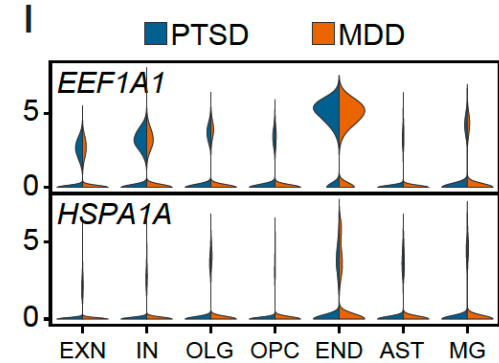
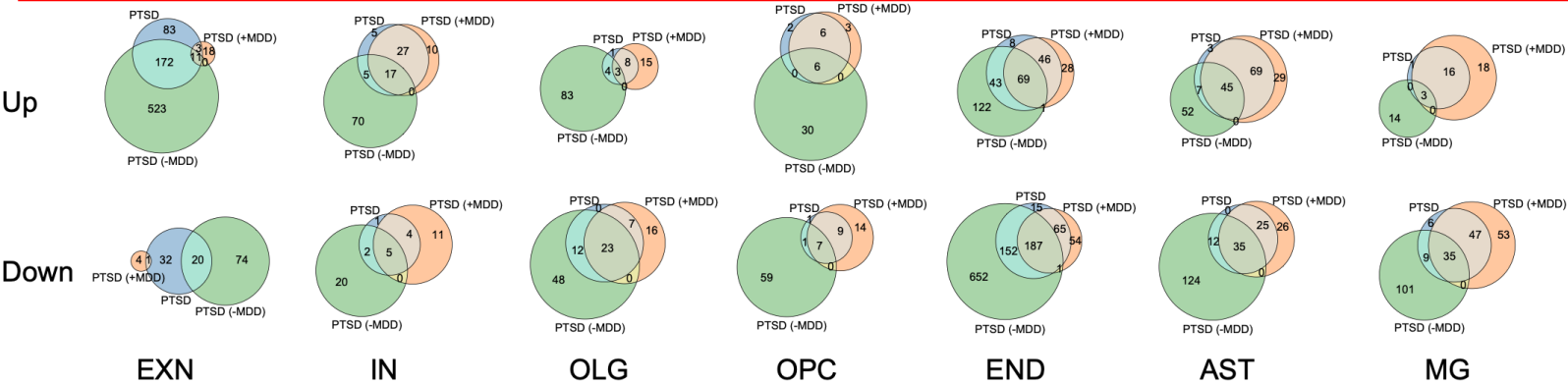
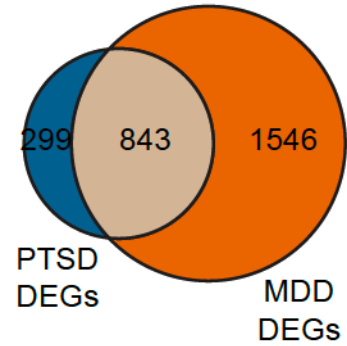
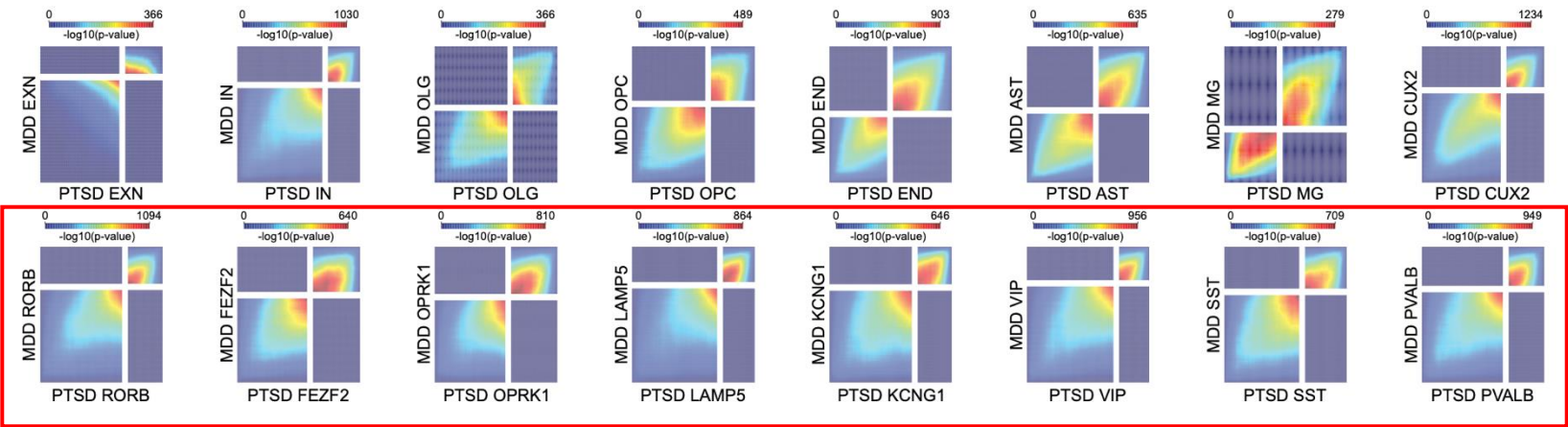
*Is this specific to PTSD?*

Are we finding disease-specific biology or shared mechanisms across psychiatric disorders?

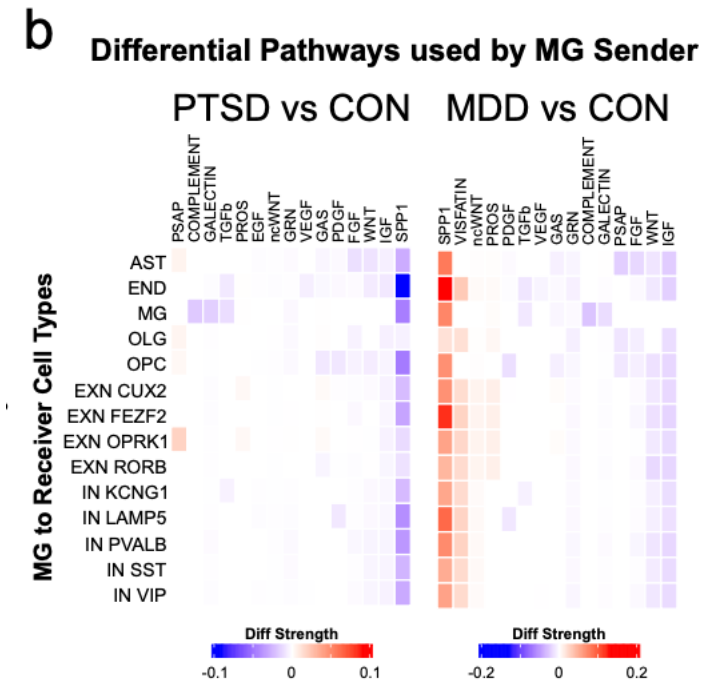
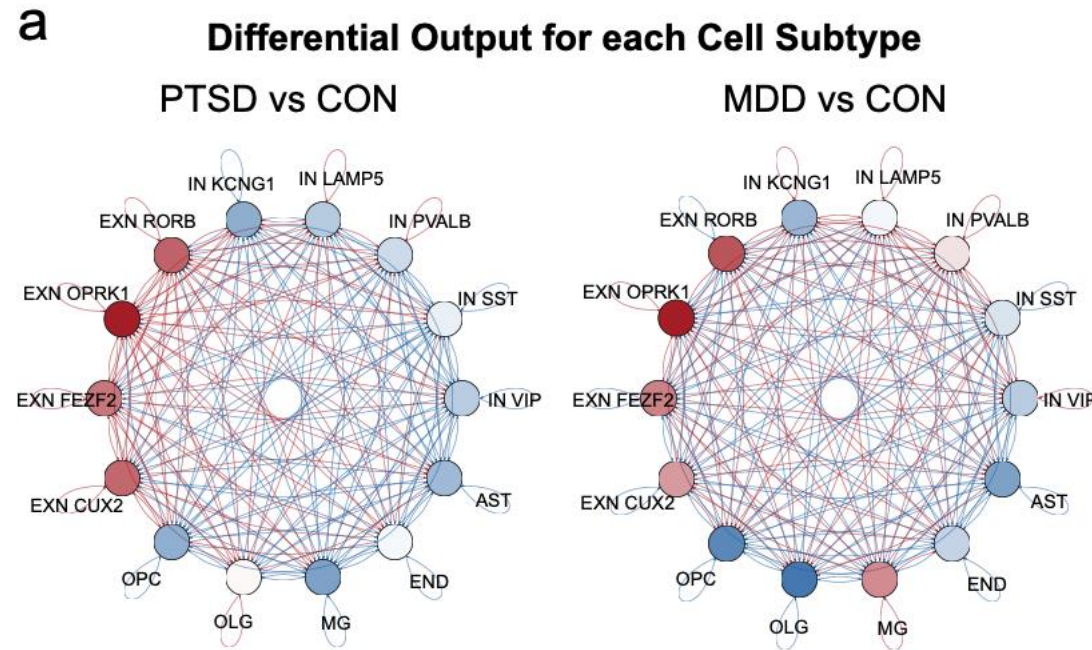
- >60% of PTSD cases are comorbid with MDD
- Shared Symptomology (e.g. anhedonia, sleep disturbances)
- Shared Neurobiological underpinnings (e.g. brain regions, neurotransmitter disruption)
- Shared Genetics (genetic correlation ~65%)
- PTSD is currently treated with antidepressants. No anti-PTSD drugs currently available.



# Gene Convergence between PTSD and Major Depression

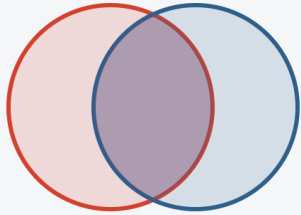


# Gene Divergence between PTSD and Major Depression is related to immune cell communication



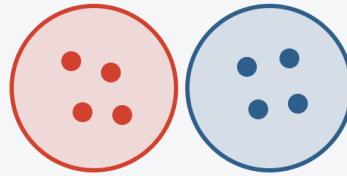
# What does this tell us about PTSD?

● PTSD ● MDD



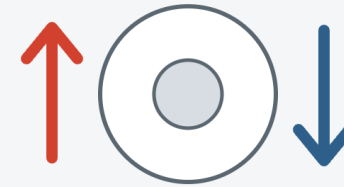
## Some molecular changes are shared

PTSD and MDD share many gene-expression changes, consistent with overlapping biology across psychiatric disorders.



## Some changes are distinct

Specific gene-expression differences distinguish PTSD from MDD in both neurons and immune cells

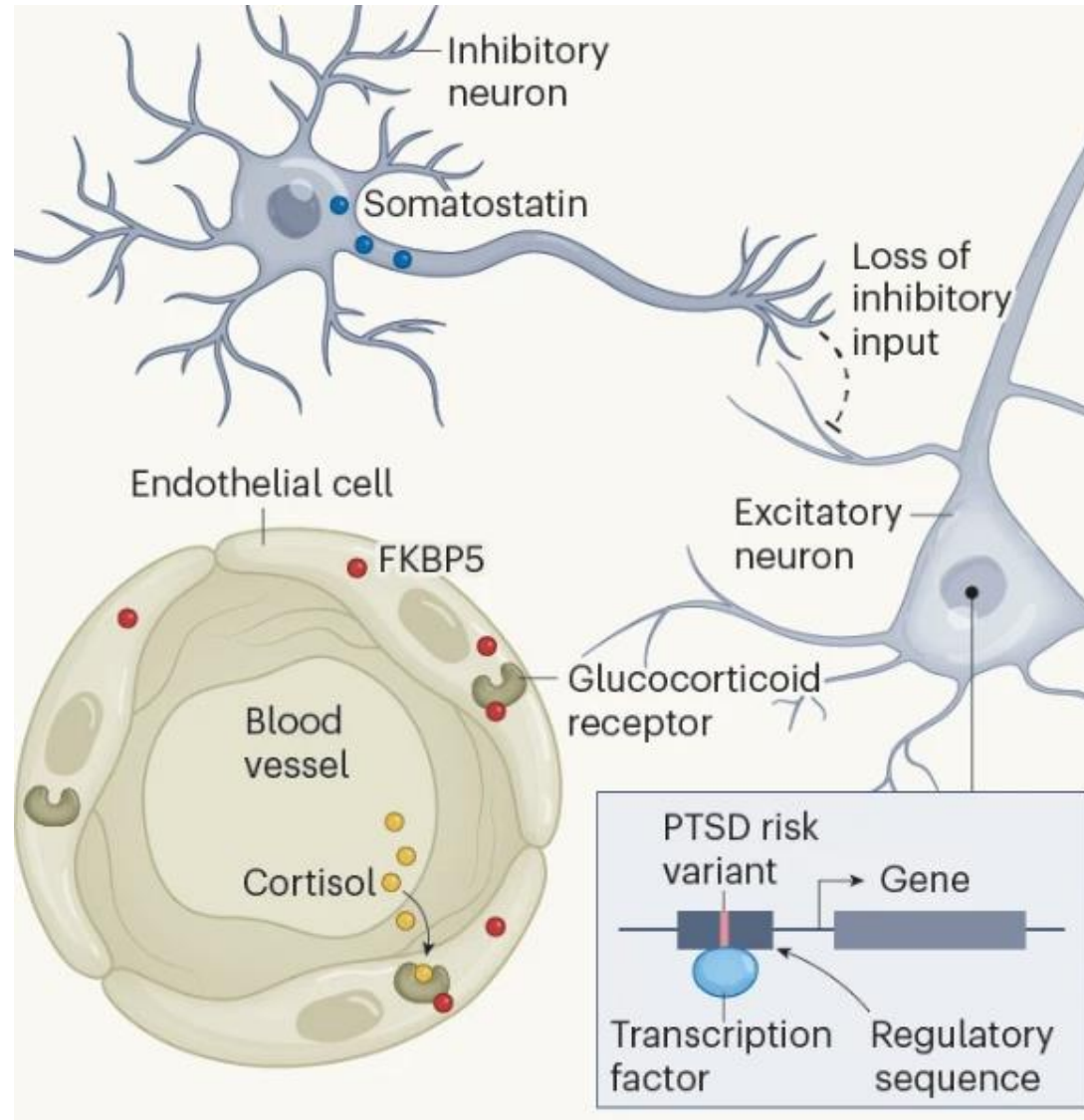


## Cell identity matters

Within the same cell type, PTSD and MDD can show different, and sometimes opposite, gene-expression changes.

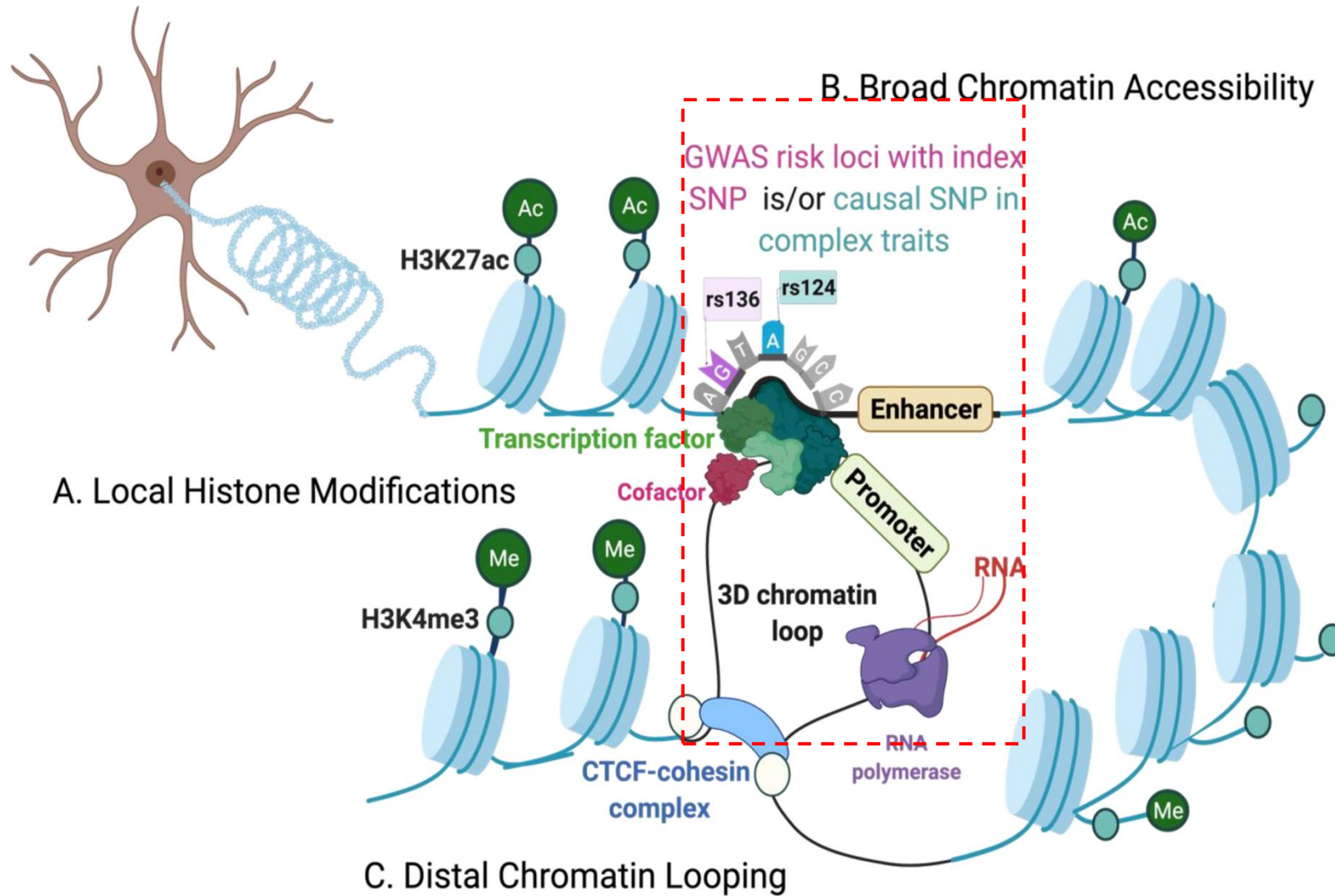
*Psychiatric disorders can share biology without being biologically identical*

# PTSD is a cell-specific disorder of the human brain



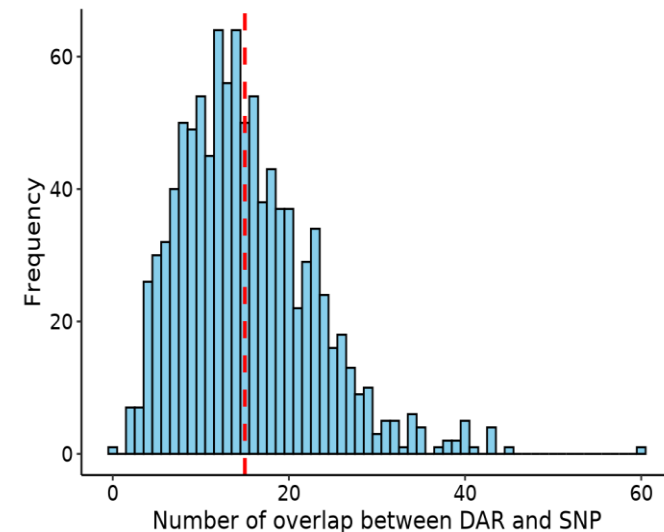
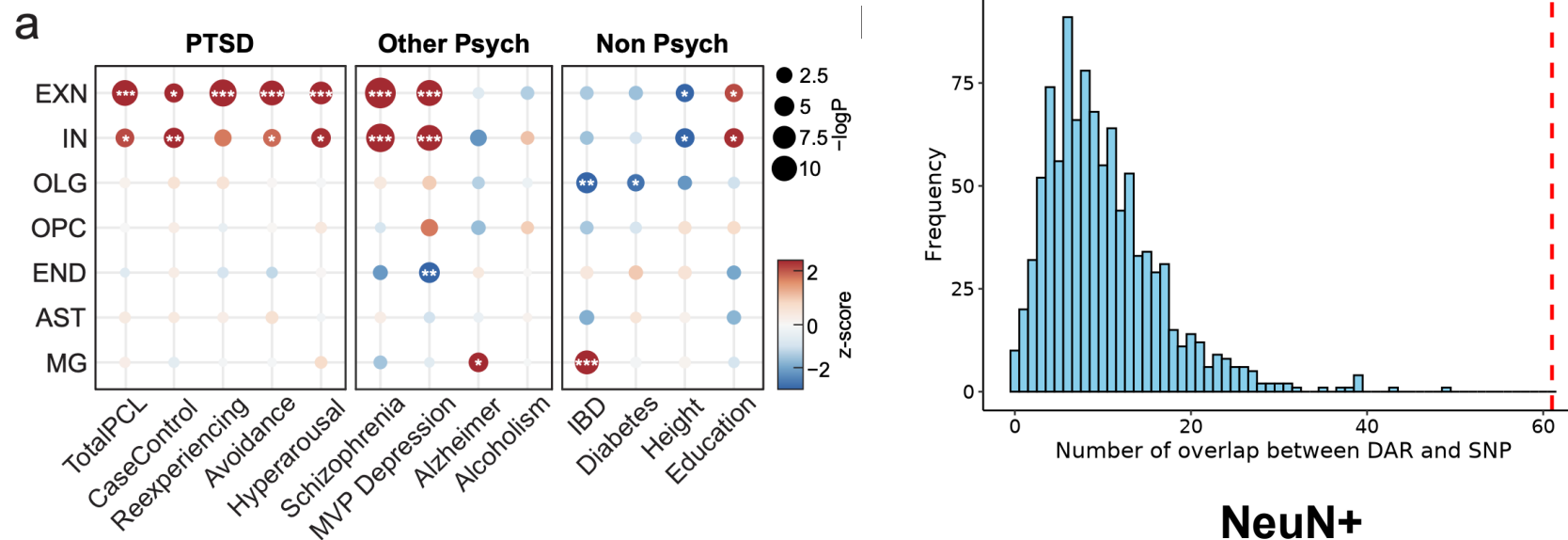
*But **why** are these cell types vulnerable?*

# From Disease Biology to Genetic Mechanism



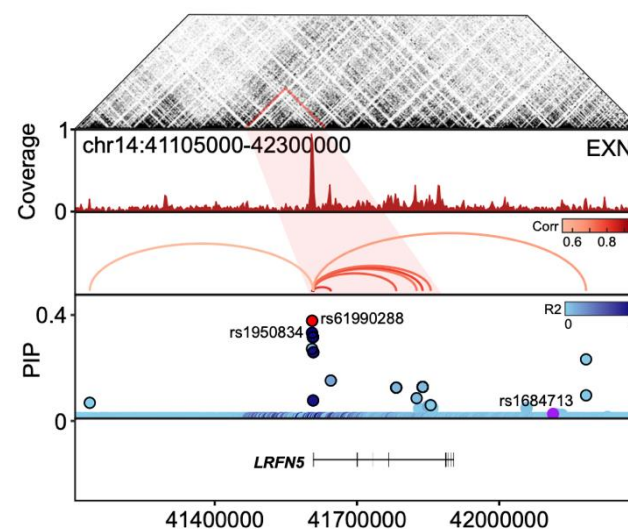
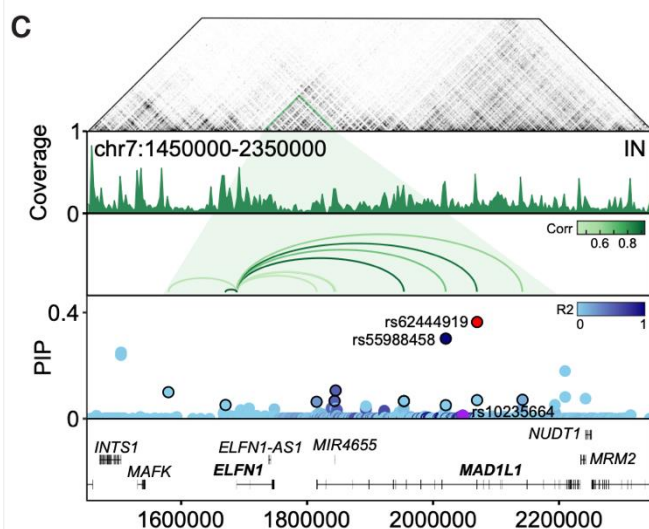
*Where in cells does PTSD risk actually act?*

# PTSD Risk Occurs in Neurons



NeuN+

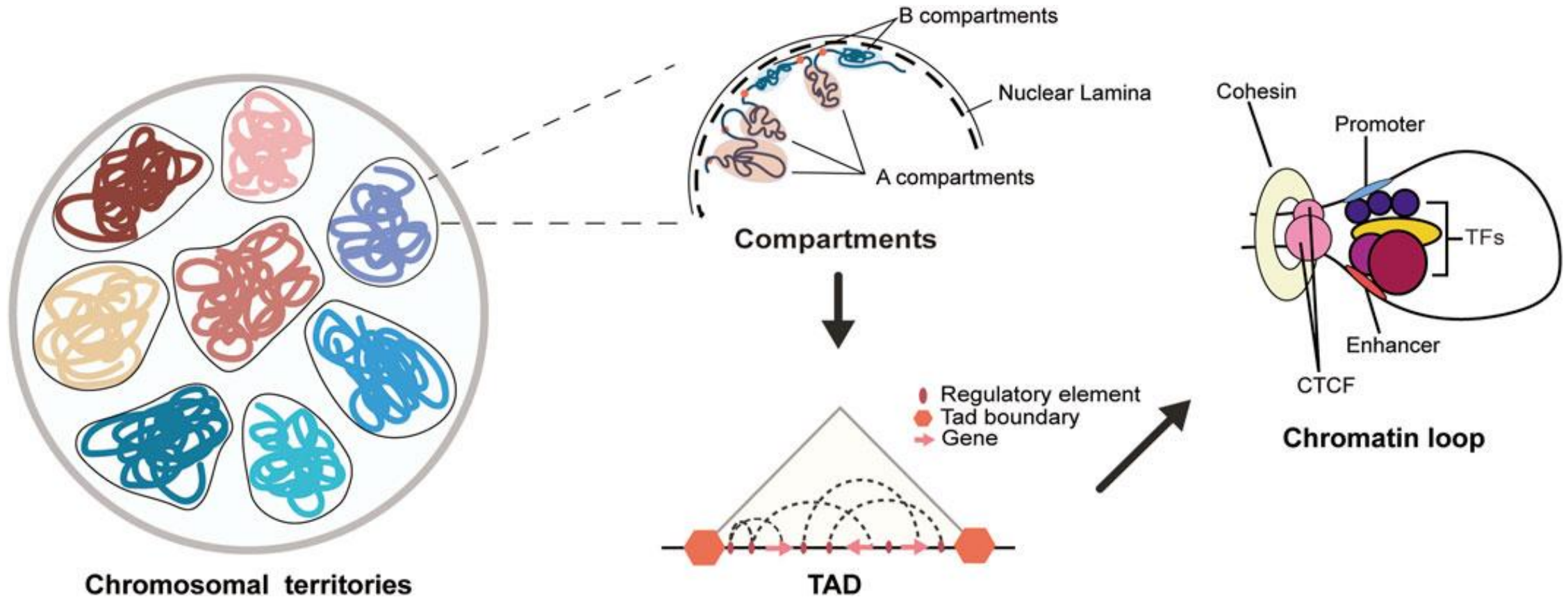
NeuN-



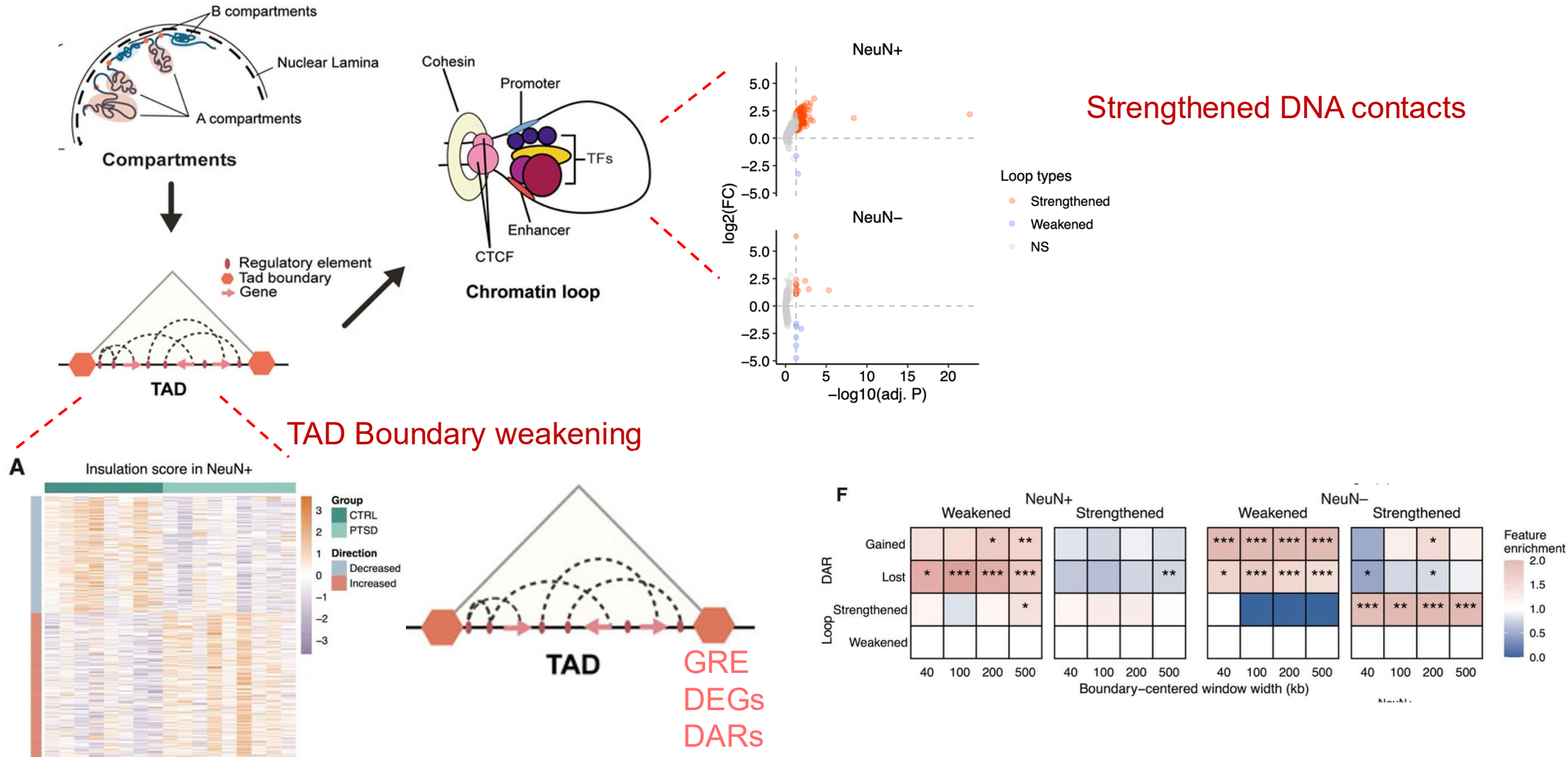
Duan et. al. in review  
Hwang, Skarica, Xu et. al. 2025

The goal of fine-mapping is to identify the **genetic variants** that **causally** affect PTSD.

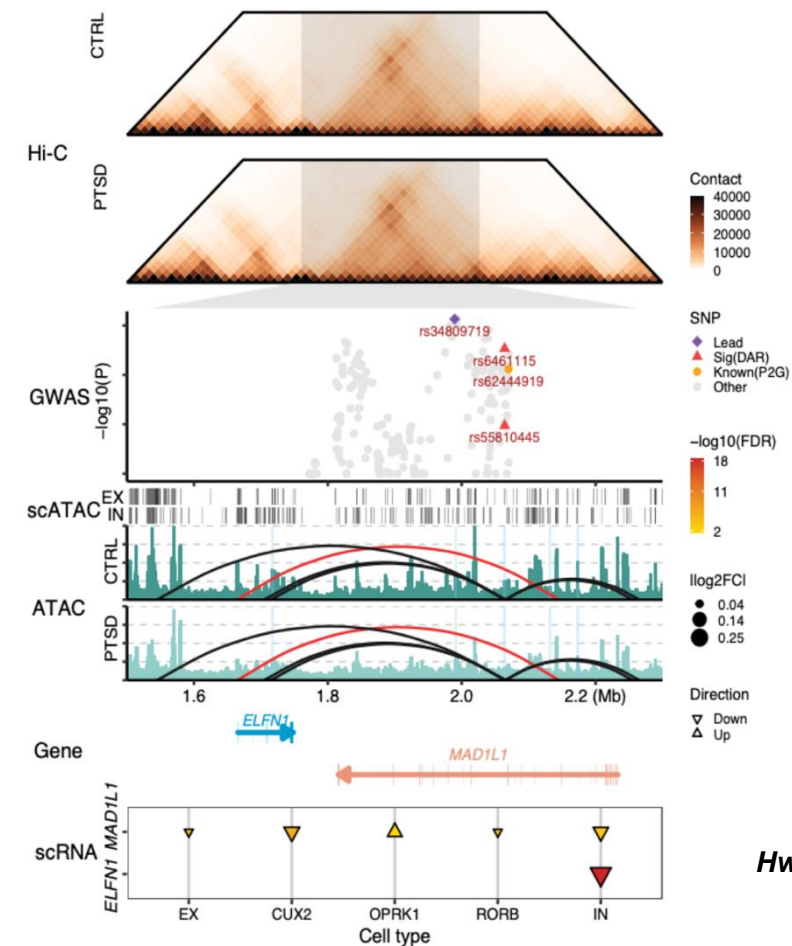
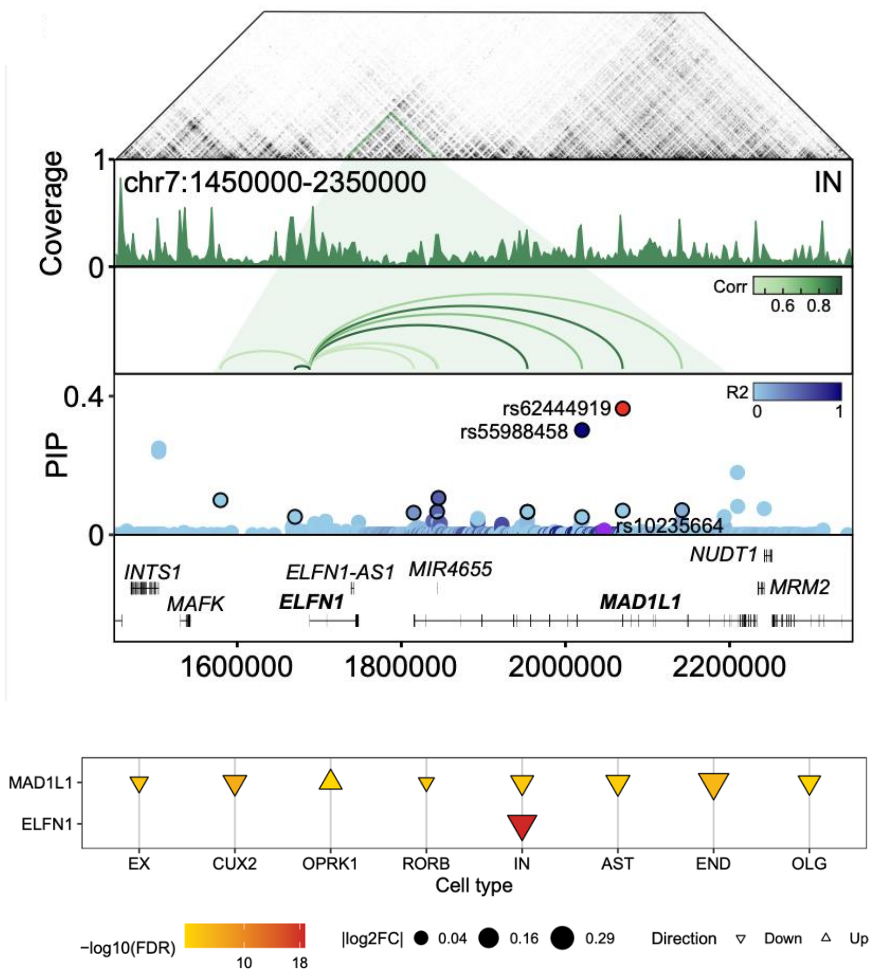
# The 3D DNA Problem



# The PTSD 3D DNA structure is altered by stress hormones



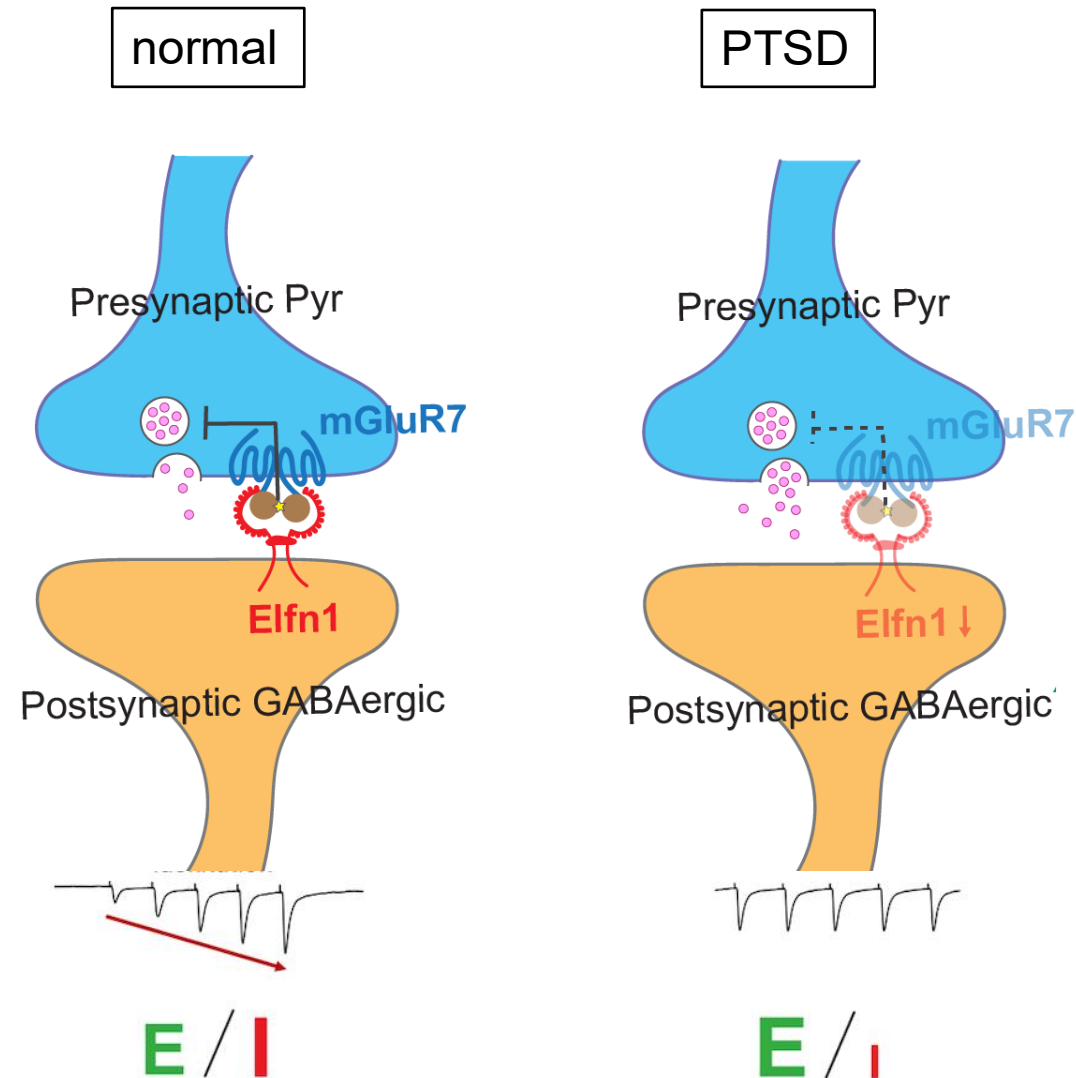
# Significant increases in DNA contacts between *MAD1L1* and *ELFN1* suggest genetic regulation of activity



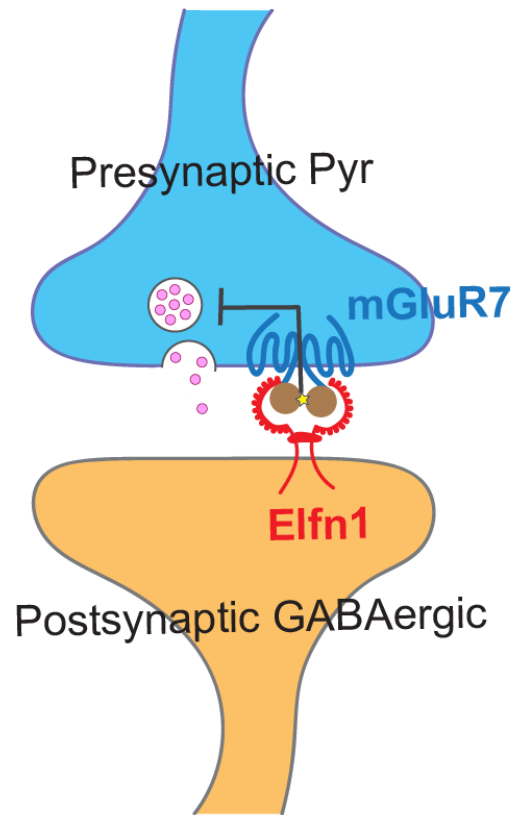
Hwang, Skarica, Xu et. al. 2025

Duan et. al. In Review

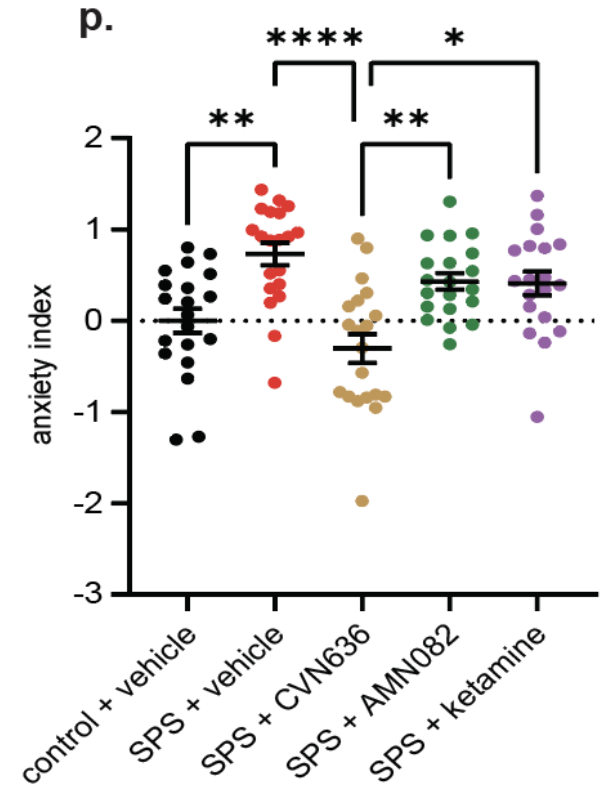
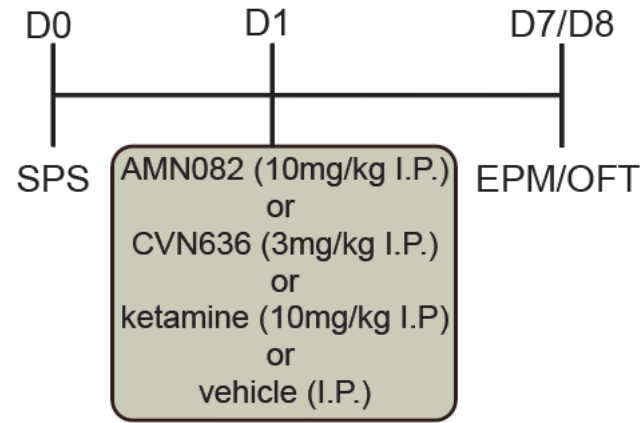
# Decreased Elfn1/mGluR7 leads to decreased inhibition onto excitatory neurons



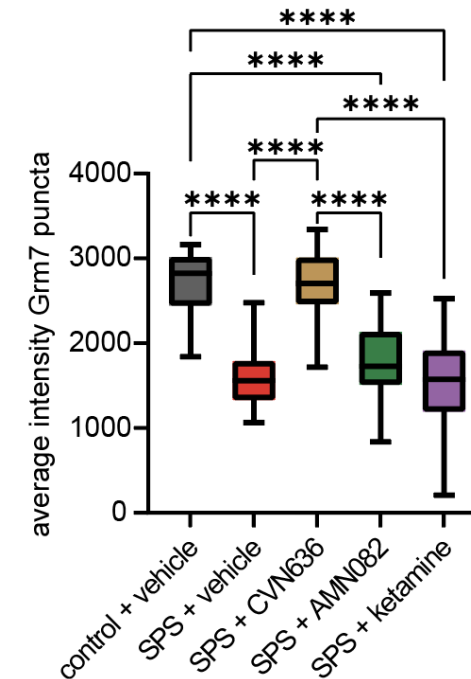
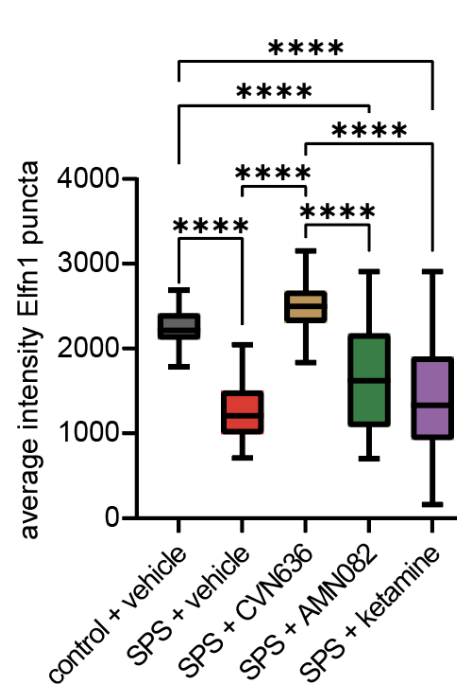
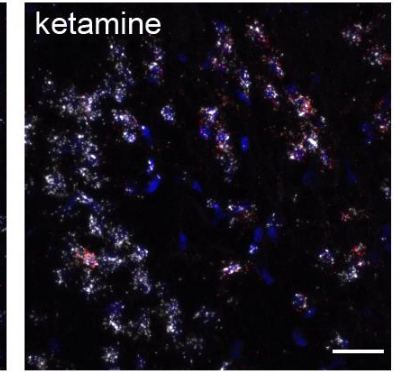
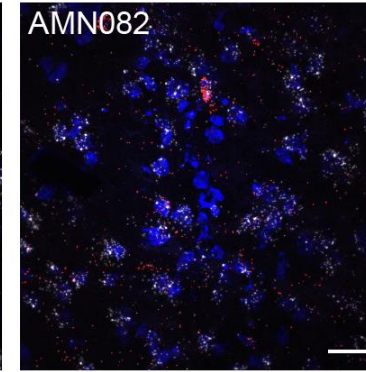
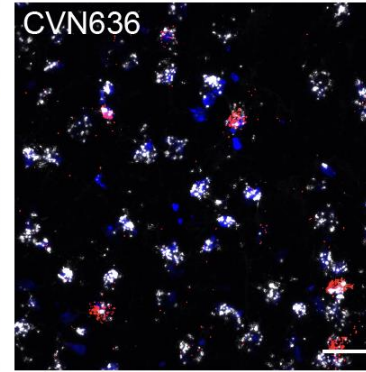
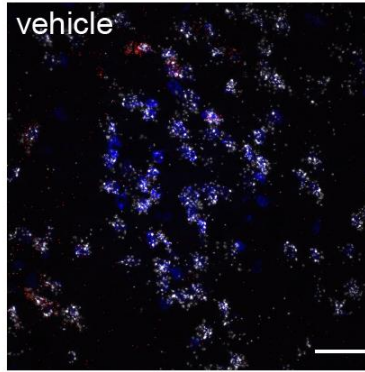
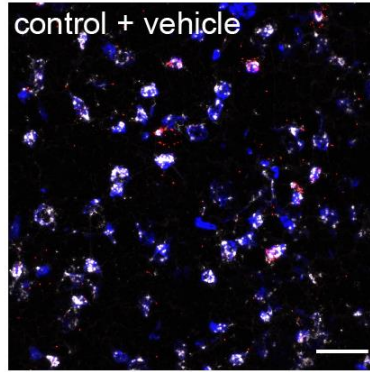
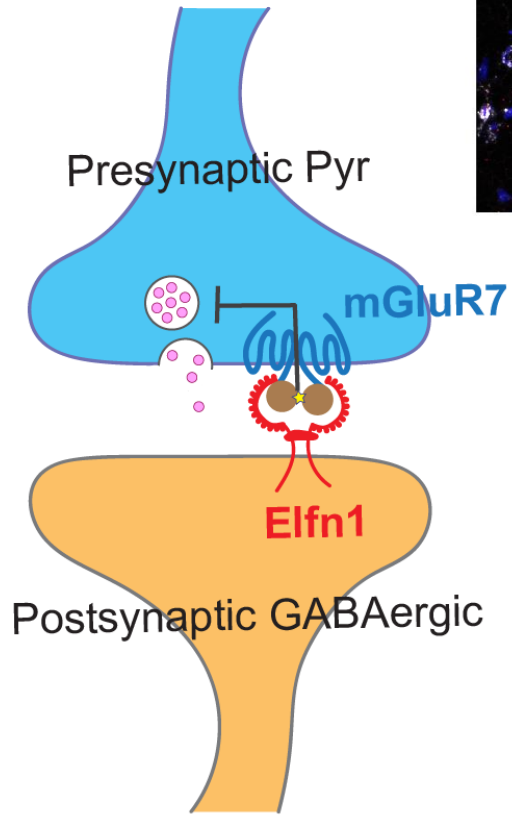
# mGluR7 agonists alleviate anxiety-like behavior after traumatic stress



CVN636 and AMN082:  
mGluR7 allosteric agonists



# mGluR7 agonists alleviate anxiety-like behavior after traumatic stress



CVN636 and AMN082:  
mGluR7 allosteric agonists

# A genomic discovery becomes a therapeutic hypothesis



## Identify genetic risk

A PTSD-associated genetic signal

***MAD1L1* risk loci**



## Connect risk to gene regulation

Cell-specific chromatin and 3D DNA interactions implicate candidate genes, including ***ELFN1***



## Define a biological mechanism

Investigate how ***ELFN1***-related signaling may influence neuronal communication

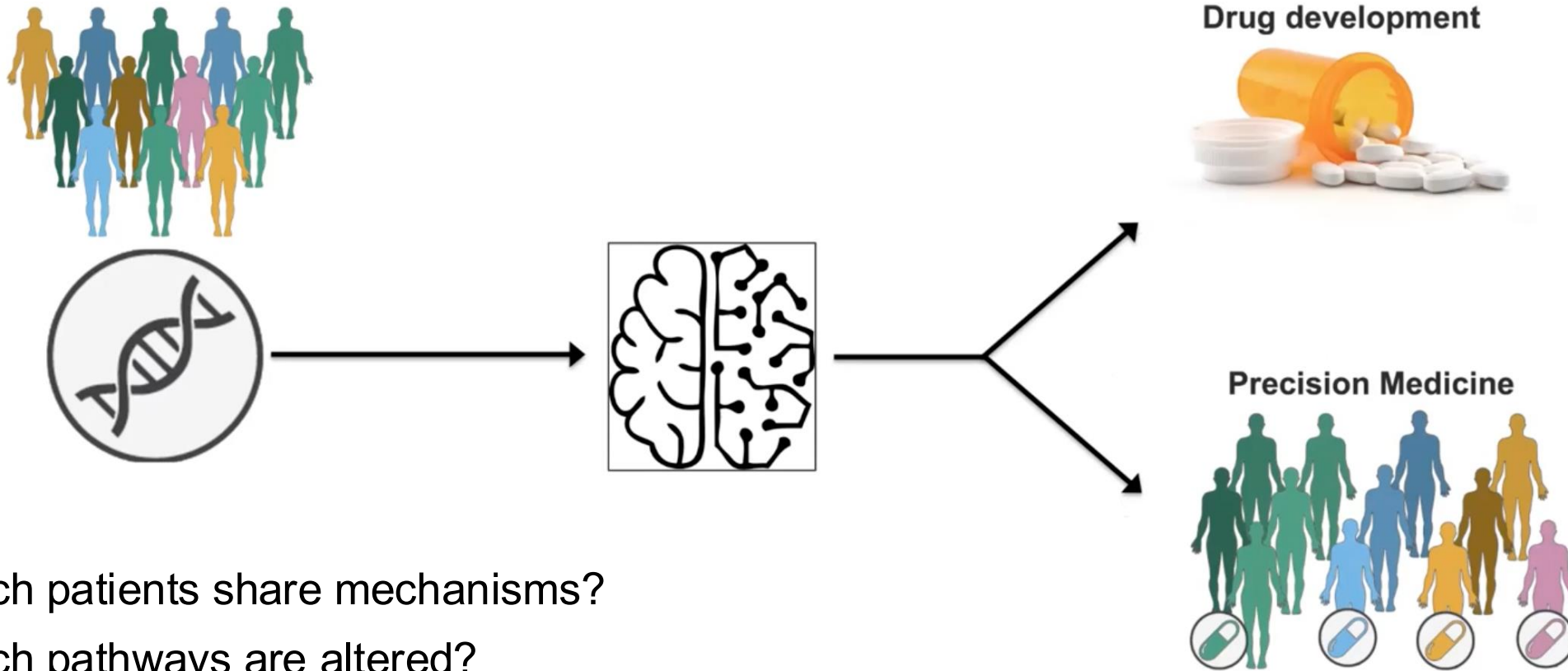
***ELFN1*–mGluR7 signaling across inhibitory and excitatory neurons**



## Test ways to modify the biology

Ketamine  
mGluR7 agonist

# What does this mean for people with PTSD?



- Which patients share mechanisms?
- Which pathways are altered?
- Which cell types are involved?
- Which existing drugs might be repurposed?
- Which new targets should be developed?

# SIGNIFICANCE

Can molecular biology help us identify biologically distinct forms of psychiatric illness?

1. **Psychiatric genetic risk must be interpreted in the context of specific brain cells.**
2. **PTSD associated changes extend beyond neurons to vascular and immune-related cell populations**
3. **Single-cell functional genomics can connect genetic variation to regulatory mechanisms and altered neuronal communication.**
4. **Shared and distinct molecular signatures may help explain biological overlap and differences across psychiatric disorders**
5. **This framework prioritizes candidate mechanisms for functional validation and future therapeutic discovery**

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Jiarui Chen  
Eliska Pritulva

Alicia Che, PhD  
John Krystal, MD  
Jensine Coudriet  
Keith Young  
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